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SCIATICA: TREATMENT WITH EPIDURAL INJECTIONS OF PROCAINE AND HYDROCORTISONE

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INJECTION of procaine hydrochloride containing hydrocortisone acetate into the epidural space via the sacral hiatus helps to relieve sciatica. The purpose of this report is to review the history, technic, results of, and indications for this type of treatment.

History

The use of the epidural space as a site for the introduction of a therapeutic agent is not new. In 1901, Cathelin,[1] reported injecting cocaine through the sacral hiatus in patients with pain of inoperable rectal carcinoma. In 1928, Viner[2] reported the similar use of procaine in Ringer's solution to treat sciatica. In 1953, according to Cappio,[3] Lièvre and his associates in France reported the introduction of hydrocortisone by the same route on 20 patients. Because of the encouraging results, there have been many published reports from abroad. Recently, Brown[4] in this country reported 62 cases with excellent results.

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In 1950, we began to treat sciatica with occasional success by introducing 100 ml. of isotonic saline solution through the sacral hiatus. Later on, a smaller quantity of hypertonic saline solution was submitted and procaine hydrochloride was added to reduce the pain of injection. This did not seem to improve the results, so procaine alone was used, followed by straight-leg raising exercises. During the last five years the volume of procaine solution has been reduced to 30 ml. and hydrocortisone acetate has been added with improvement in the results.

Indications

The main indication is sciatica of a character indicating pathologic involvement of the spinal nerve roots that contribute to the sciatic nerve. The clinical picture may suggest a protruded or degenerated disk, radiculopathy, adhesions following laminectomy, arthritis, trauma, or sciatica with no demonstrable cause. Nocturnal gastrocnemius cramps, which may follow an otherwise successful operation for protruded disk, are also an indication. As is to be expected, sciatica due to carcinoma with bone metastasis, intradural or extradural tumor, arachnoiditis, postherpetic or diabetic neuralgia is not benefited by this therapy.

Technic

The nerve roots that are responsible for pain in the sciatic distribution* may be reached by injection of 30 ml. of a fluid into the epidural space via the sacral hiatus *(Fig. 1 A and B)*. The technic of introducing the needle is the same as that for caudal anesthesia. Thirty milliliters of 1 per cent procaine hydrochloride is mixed with 125 mg. of hydrocortisone acetate. Three injections are given on consecutive or alternate days. Patients are instructed in straight-leg raising exercises while the analgesic effect of the procaine is still present *(Fig. 2)*.

Complications rarely ensue from sensitivity reactions to procaine or to the corticosteroid. Accidental introduction of the procaine into the dural sac has not occurred. Aggravation of the pain during the injection usually is considered a good prognostic sign, and requires merely a reduction of the rate of injection.

Results

Our series comprises 239 patients, the youngest of whom was 20 and the oldest 75 years of age. Patients with more than 60 per cent relief for three months or longer were classified as having good results. Those with from 40 to 60 per cent relief, as having fair results, and those who had return of pain in less than three months, or less than 40 per cent relief, were considered as having poor results. Of 239 patients, 58 per cent had good results, 8 per cent fair results, and 34 per cent poor results. Eight of those with good relief but with recurrence after three

* *For pain at a higher level, the needle may be passed between the laminae into the epidural space.*

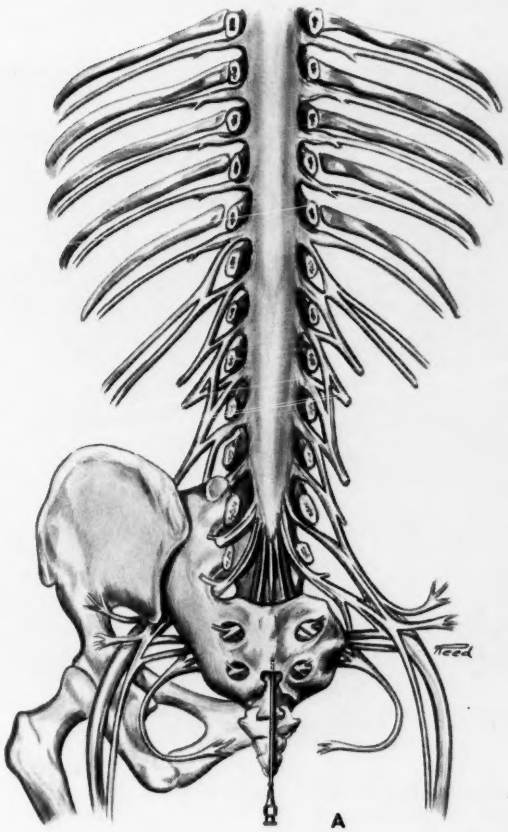

Fig. 1. A, Sketch showing placement of the needle into the epidural space through the sacral hiatus.

months had a subsequent series of injections with relief again. One hundred fifteen of these patients had one or more laminectomies before this therapy was begun. Of these, 56 per cent had good results, 11 per cent had fair results, and 33 per cent had poor results. Of the remaining 124 patients, 60 per cent had good, 8 per cent fair, and 32 per cent poor results. For analysis of results see *Table 1.*

Comment

In attempting to evaluate the reason for relief of pain, these facts about the pathophysiology of nerve root compression and postoperative pain were uncovered.

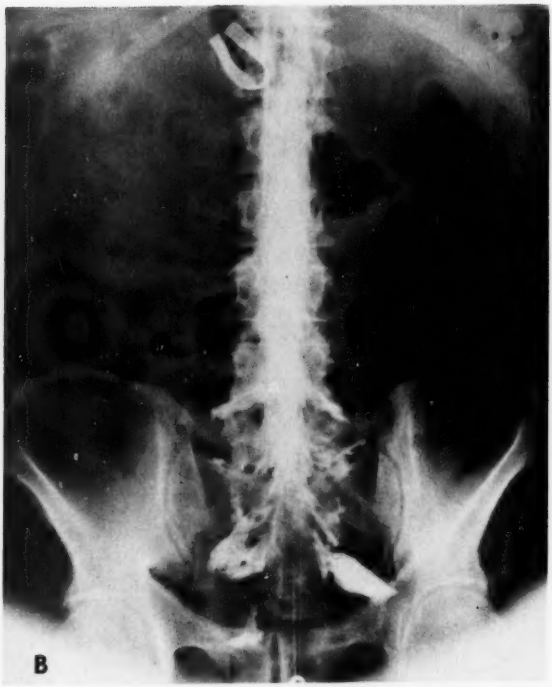

Fig. 1. B, Roentgenogram showing the distribution of contrast medium (30 ml.) after epidural injection (demonstrated in a fresh cadaver).

Lindahl and Rexed[5] demonstrated by biopsy of the dorsal root that 7 of 10 patients with nerve root compression had infiltration of lymphocytes and edema of the nerve. Also it is well known that adhesions follow hemorrhage and trauma anywhere in the body; the nerve sleeve is no exception. During operation for the removal of protruded disk, by necessity the epidural fat is traumatized or removed, and fibrous tissue replaces it. This limits the normal excursion of the nerve which is produced by movement of the back and legs. Greenwood, McGuire, and Kimbell[6] noted on re-exploration that one third of laminectomy failures were due to extradural adhesions.

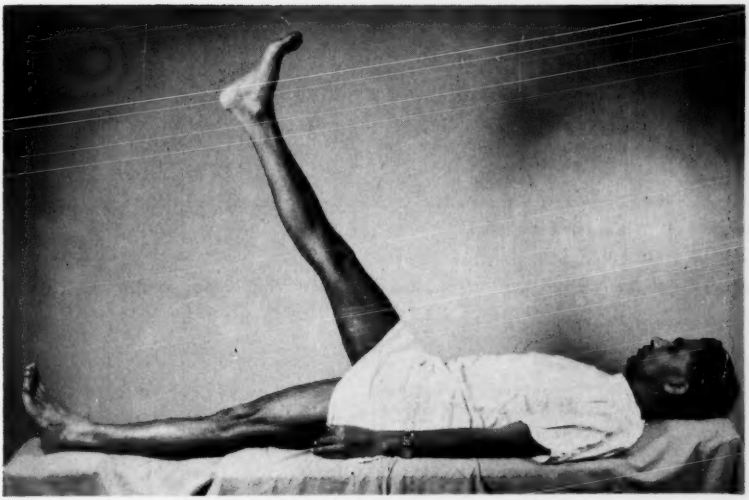

Fig. 2. Straight-leg raising after epidural injection.

Thus, we believe that sciatica that is not due to pressure on the nerve root, is due to inflammation, edema, or adhesions around the nerve sleeve. By bathing the pathologic nerve root with a solution of procaine containing a corticosteroid, the swelling and inflammation responsible for the pain can be reduced and the nerve mobilized by straight-leg raising exercises.

Conclusions

Data are presented to show that epidural injections of procaine hydrochloride and hydrocortisone acetate followed by straight-leg raising exercises are helpful in the relief of sciatic pain. Of 239 patients treated, more than half were benefited.

Table 1.—*Results in 239 patients with sciatica treated with epidural injections of hydrocortisone acetate in procaine hydrochloride and straight-leg raising exercises*

(Follow-up period—three months to five years)

Sciatica	Results, number of patients			Total numbers of patients
	Good *	Fair †	Poor ‡	
Persistent or recurrent after lumbar laminectomy	62	12	41	115
Cause undetermined	75	9	40	124
Total	137	21	81‖	239

* Good—60 to 100 per cent relief

† Fair —40 to 60 per cent relief

‡ Poor —Less than 40 per cent relief, or recurrence within three months.

‖ Analysis of poor results:

Subsequently relieved by		
removal of protruded disk	22	
removal of infected disk	1	
intradural injection	22	
		45
Unrelieved		
conversion reaction	8	
reason undetermined	28	
		36
Total		81

Although the results are difficult to evaluate, since pain is a subjective phenomenon, we believe that the procedure outlined is effective therapy.

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CORTICOSTEROIDS* ADMINISTERED INTRADURALLY FOR RELIEF OF SCIATICA

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IT has been shown that 58 per cent of patients with sciatica due to extradural adhesions may be benefited by hydrocortisone in one per cent procaine hydrochloride solution injected into the epidural space via the sacral hiatus.[1] This injection is accompanied by straight-leg raising exercises designed to mobilize the nerve roots. When this extradural treatment fails, or in cases where the causative lesion is known or presumed to be in the subarachnoid space, we have injected corticosteroids intradurally by lumbar puncture. The early results have been encouraging.

Material

Thirty-six patients with sciatica have received intradural (subarachnoid) injections of corticosteroids. The average duration of sciatica was three and one-half years, and all required analgesics for pain. Twenty-nine patients had one or more myelograms prior to the treatment, and in five a second myelogram was followed by an immediate and continuing increase of pain. Twenty-eight patients had undergone one or more laminectomies, twenty-five had received extradural injections of hydrocortisone in procaine, two had received corticotropin (ACTH) intravenously, and five had received corticosteroids orally—all with little or no benefit. In eight patients, arachnoiditis was confirmed at operation before the intradural injections were given.

After a preliminary trial of corticosteroids in other forms, methylprednisolone acetate‡ was selected as the least irritating and longest acting preparation for subarachnoid administration.

Method

With the patient lying on his side, lumbar puncture is performed, and from 40 to 80 mg. of methylprednisolone acetate is injected *(Fig. 1)*. If the patient's pain is aggravated by straight-leg raising, 50 mg. of procaine hydrochloride crystals in 3 or 4 ml. of cerebrospinal fluid is then injected. The patient is turned on his back, and straight-leg raising exercises with jugular compression *(Fig. 2)* are carried out in an effort to mobilize the nerve roots and to disseminate further the therapeutic agent. After three hours the patient is discharged to his home and is advised to resume normal activity. In instances in which there is only partial relief of pain, the injection may be repeated.

* *The drugs used in this study were kindly supplied in part by The Upjohn Company, 301 Henrietta Street, Kalamazoo 99, Michigan.*

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‡ *Depo-Medrol (methylprednisolone acetate in sodium chloride), The Upjohn Co.*

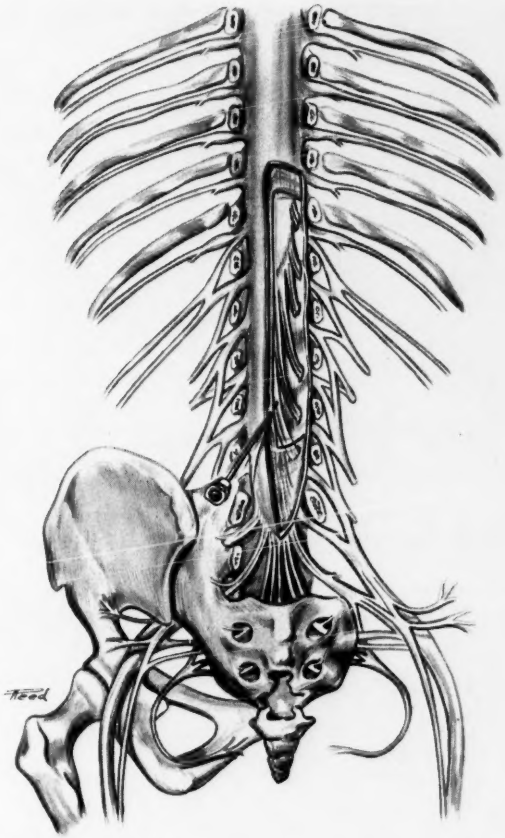

Fig. 1. Sketch showing placement of the needle into the subarachnoid space so that the therapeutic agent may follow the naked nerve roots into their dural sleeves.

Results

A follow-up of from 2 to 11 months has disclosed complete relief of sciatica in 14 patients and at least 50 per cent relief in 12 *(Table 1)*. These 26 patients were able to resume their daily work without need for analgesics. Ten patients had little or no relief. In two of these, cerebrospinal fluid was not encountered at lumbar puncture presumably because of obliteration of the subarachnoid space by arachnoiditis. There is thus no proof that an intradural injection was accomplished. In two patients unrelieved, subsequent psychiatric diagnosis was "conversion reaction."

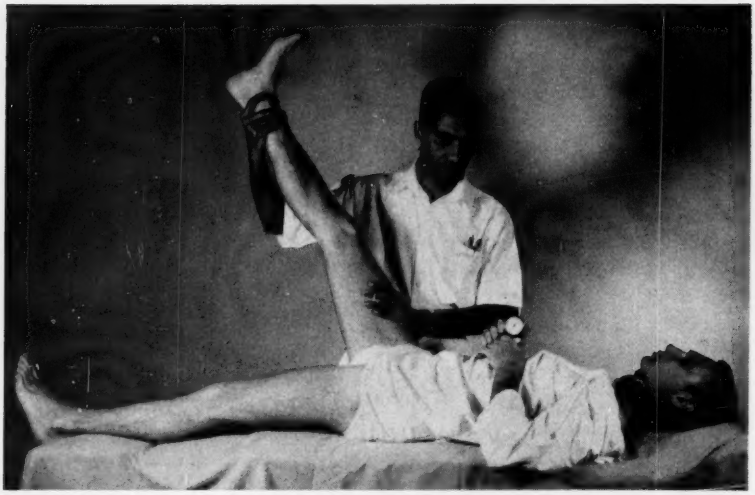

Fig. 2. Straight-leg raising combined with jugular compression to stretch subarachnoid adhesions and to encourage further dissemination of the therapeutic agent.

Table 1.—*Data on 36 patients with sciatica treated by intradural injections of corticosteroids*

Brand of corticosteroid	Each dose, mg.	Injections, total number	Transient severe pain in legs	Results, number of patients		
				Good	Fair	Poor
Hydrocortone†	100	4	1	0	2	1
Solu-Cortef‡	100	11	3	1	3	3
Solu-Medrol‡	40 to 80	21	7	6	5	4
Depo-Medrol‡	40 to 80	12	0*	7	2	2
		Total	11	14	12	10

*An additional 40 patients have since received Depo-Medrol without clinical reaction, but with occasional transient pleocytosis.

†Merck, Sharp & Dohme.

‡The Upjohn Company.

Cell counts and protein estimations of the cerebrospinal fluid were made in several instances at various intervals after injection, and seldom showed significant change. Prompt clinical reactions consisting of intermittent, spasmodic, severe pain in the lower back and in the legs occurred in 11 patients. These symptoms

cleared in from two to three hours and did not affect the final result. They may have been due to substances added to increase the solubility of the corticosteroid since they have not occurred with the use of methylprednisolone acetate that contains no such substances.

Discussion

Intradural adhesions may result from nerve root compression, from trauma, surgical and otherwise, and from myelography, particularly when blood also is present in the subarachnoid space. Corticosteroids, by their antiinflammatory and antiallergenic action, reduce congestion and inflammation. Hydrocortisone, particularly, inhibits the development of foreign-body giant-cell granulomata and fibrous tissue that produces the piarachnoidal adhesions[2] from retained contrast medium or from trauma. The effect of corticosteroids on mesodermal elements (of which the arachnoid is one) is a direct one, and local application is more effective than is the systemic.[2]

Aside from the transient reactions described, no harmful effects followed single or repeated intrathecal injections of corticosteroids. Tissue study in experimental animals by Feldman, Behar, and Samueloff,[2] and clinical and pathologic study by Pieper and Fields[3] of patients treated for amyotrophic lateral sclerosis, likewise have revealed no harmful effects on the piarachnoid or nerve roots.

Conclusion

The intradural administration of corticosteroids has been used in 36 cases of sciatica presumed to be due to intradural lesions. The preliminary results, we believe, justify the cautious use of this therapy in carefully selected cases.

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THE DETERMINATION OF BLOOD AMMONIUM BY A MODIFICATION OF THE CONWAY TECHNIC

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SINCE the latter part of the nineteenth century the existence of ammonium in normal circulating blood has been questioned from time to time. Now it is generally agreed that minute amounts of certain substances do exist in the blood, which appear as gaseous ammonia after alkalization of the blood sample. This base is present in two forms: the ammonium ion, NH_4^+, and free ammonia, NH_3. The relationship between the two forms may be represented by the equation

$$NH_3 + H^+ \rightleftharpoons NH_4^+$$

Because a proton is involved, the equilibrium is sensitive to pH and might be expected to shift greatly in pathologic conditions characterized by acidosis or alkalosis. Evidently this does not occur. According to Bessman,[1] even at the extremes of physiologic pH variation more than 99.9 per cent of this base is in the form of the ion. Thus the term *ammonium* is preferable to *ammonia,* and will be used throughout this report to signify the summation of both forms.

Numerous methods for the quantitative estimation of ammonium in blood have been devised and have been presented in the chemical and medical literature.[2-4] The accurate determination of the minute amounts of ammonium that exist in blood is difficult by any technic because of certain potential and subtle sources of error. The four principal sources of unreliability in all methods are: (1) minuteness of quantities of ammonium present in the blood; (2) ease of contamination of the specimen; (3) continuous increase of ammonium in blood after its withdrawal from the body; (4) alkaline hydrolysis of labile ammonia-producing compounds.

In any blood specimen, even one in which the ammonium concentration is high, only microgram quantities are present. For this reason, any practicable method of analysis must be extremely sensitive, and therein lies its vulnerability to contamination. Infinitesimal amounts of ammonia in the laboratory air, from reagents, from urine specimens, or even tobacco smoke are potential contaminants. Furthermore, in any of the methods that depend upon the basicity of ammonia for measurement, errors may arise through trace quantities of soaps, detergents, or other nonvolatile alkalies in the glassware used for the tests.

Conway[2] on the basis of his experimental work stated that blood at the instant of withdrawal from the body contains no ammonium, but that ammonium is produced rapidly during the first five minutes and then more slowly for many hours afterward. In 1954, McDermott, Adams, and Riddell[5] called attention

to the early, rapid release of ammonium from blood of cirrhotic patients, and attributed this largely to the rapid breakdown of unstable compounds, particularly adenosine. In 1957, Seligson and Hirahara[3] presented convincing clinical evidence that ammonium is actually present in freshly drawn blood. Whatever the initial concentration, there is little doubt that blood ammonium concentration becomes greater on standing, though the rate of increase varies from sample to sample.

The fourth cause of error in measurement arises from the susceptibility of unidentified ammonia-producing compounds of blood to alkaline hydrolysis, as demonstrated by Seligson and Hirahara.[3] This can lead to erroneously high results in the determination of blood ammonium.

Attempts to measure blood ammonium by any method are somewhat arbitrary because some of the factors involved are not completely understood nor are all of them capable of being adequately controlled. However, analyses can be performed with reasonable accuracy if each of the potential sources of error is recognized and appropriately dealt with. The purpose of this report is to describe a simple and reliable modification of the Conway technic in which provision has been made to eliminate or to minimize each of the four potential sources of error. This laboratory has performed more than 1300 analyses during the two and one-half years we have used this method.

Materials

1. A microburet (capable of delivering fluid in increments of 0.0001 ml.).
2. Conway microdiffusion units *(Fig. 1)*.
3. Ostwald-Folin pipets (0.5 ml.).

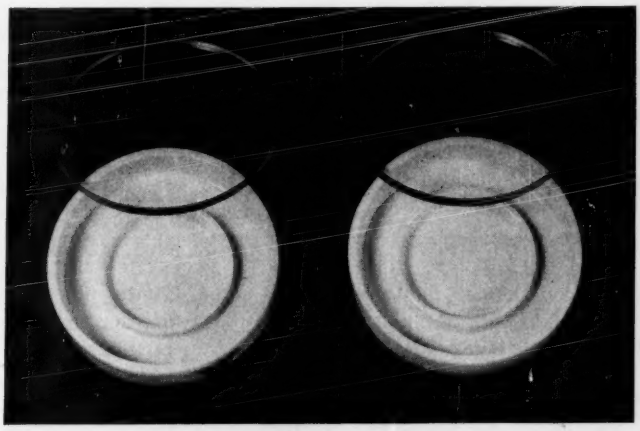

Fig. 1. Conway microdiffusion units.

Reagents

1. Hydrochloric or sulfuric acid (approximately 0.01 N, accurate standardization is unnecessary).

2. Boric acid stock solution (2 per cent).

Dissolve 10 g. of boric acid crystals in about 200 ml. of water with the aid of heat and agitation. Cool the solution to room temperature and dilute to 500 ml.

3. Bromcresol green indicator (0.1 per cent).

Place 0.1 gm. of bromcresol green crystals in 100 ml. of 95 per cent ethanol and stir until they are dissolved.

4. Boric acid-plus-indicator.

Add 12.5 ml. of the bromcresol green indicator to 100 ml. of the boric acid stock solution. Dilute to 400 ml. with water. Then adjust the solution to a yellow-green with the hydrochloric or sulfuric acid (reagent No. 1). Prepare new reagent every few weeks.

5. Buffered alkali.

Place 17 gm. of anhydrous potassium carbonate and 10 gm. of potassium bicarbonate in a beaker. Add 48 ml. of water. Stir and warm gently until all crystals have dissolved. Upon cooling, a small amount of crystalline material may precipitate which does not impair the value of the reagent.

6. Ammonium sulfate stock solution [0.300 mg., ammonium-nitrogen per milliliter (NH_4^+-N/ml.)].

Dissolve 0.1415 gm. of ammonium sulfate in a few milliliters of water. Transfer the solution quantitatively to a 100-ml. volumetric flask and dilute to the mark. This solution is stable indefinitely if stored in a refrigerator.

7. Ammonium working standard (300 μg. of NH_4^+-N/100 ml.)

Pipet 1 ml. of the ammonium sulfate stock solution into a 100-ml. volumetric flask and dilute to the mark. This standard may be kept at room temperature but should be made up every few weeks.

8. Ucon lubricant, 75-H-90,000.*

Procedure

1. Draw about 2 ml. of blood into a clean dry 5-ml. syringe containing 1 drop of liquid sodium heparinate.† Cap the syringe and mix the blood with the heparin. Leave the specimen in the syringe (at room temperature) until time for analysis.

2. Apply Ucon lubricant lightly to the rims of four Conway units.

3. Place 1 ml. of boric acid-plus-indicator in the central compartments of the units. If the acid changes color, remove the acid by aspiration and add a fresh portion. Repeat this procedure until no color change occurs.

* *Supplied through the courtesy of the Carbide and Carbon Chemicals Company, 30 East 42d Street, New York 17, New York.*

† *Organon, Inc.*

4. Pipet 0.5 ml. of buffered alkali into the outer compartments of the units. Keep this reagent confined as well as possible to a small portion of the circumference. Avoid contamination of the central compartments with the alkali.

5. Twenty minutes after collection of the blood specimen, mix it gently in the syringe and dispense it into a 5-ml. beaker. With an Ostwald-Folin pipet, measure 0.5 ml. of blood into the outer compartment but on the side opposite to that of the alkali. Perform the analysis in duplicate.

6. Remove the boric acid completely by aspiration and replace it with 1 ml. of a fresh sample of boric acid-plus-indicator.

7. Place the lid on the unit and thoroughly mix the blood with the alkali by gentle manual rotation of the unit. Start an interval timer and allow diffusion to proceed for exactly 20 minutes.

8. Run ammonium standards in duplicate as described for blood. Use 0.5 ml. of the ammonium working standard. Diffuse exactly 20 minutes.

9. At the end of the diffusion period, remove the lid and, using standard acid, titrate the boric acid back to the original color. For color comparison use 1 ml. of a fresh portion of boric acid-plus-indicator in a well-rinsed unit.

10. Calculate the quantity of ammonium-nitrogen in the unknown sample by means of the equation:

$$\frac{\text{Milliliter of acid for unknown}}{\text{Milliliter of acid for standard}} \times 300 = \text{Micrograms of } NH_4^+\text{-N per 100 ml.}$$

Comment. Great sensitivity to free ammonia is an essential characteristic of any technic for the accurate measurement of blood ammonium. In this respect the modification described here is similar to most others. However, the concentration of boric acid solution, the strength of the indicator, the absolute and relative volumes of blood and alkali have all been carefully adjusted in our procedure so that optimum sensitivity and accuracy of measurement may be attained. A microburet capable of delivering titrating fluid in increments of 0.0001 ml. per scale division is an essential feature of this modification and constitutes an important factor for enhancing the accuracy of analysis. Less precise instruments should not be used.

To avoid errors from contamination of the specimen and the glassware, several precautions are taken. The blood specimen is left in the syringe until time for diffusion and is then dispensed into a thoroughly clean beaker. Boric acid is dispensed from a buret and therefore is not exposed to several, possibly contaminated pipets during the course of analysis. Finally, the Conway unit is rinsed several times with boric acid-plus-indicator in order to neutralize any trace of nonvolatile alkali in the unit before the test is started.

Evaluation of the Method

The observation of Conway[2] that the ammonium content of blood increases with the passage of time, after venipuncture, has been confirmed by others.[4,6]

However, there is no general agreement regarding the extent or the rate at which this increase takes place. Such information is of importance in establishing the greatest amount of time that could be allowed to elapse before starting the test without incurring the risk of introducing intolerable errors. To evaluate this time factor, experiments were carried out on a number of random blood samples from normal persons. Blood was drawn into heparinized syringes and remained in the syringes for the lengths of time shown in *Figure 2*.

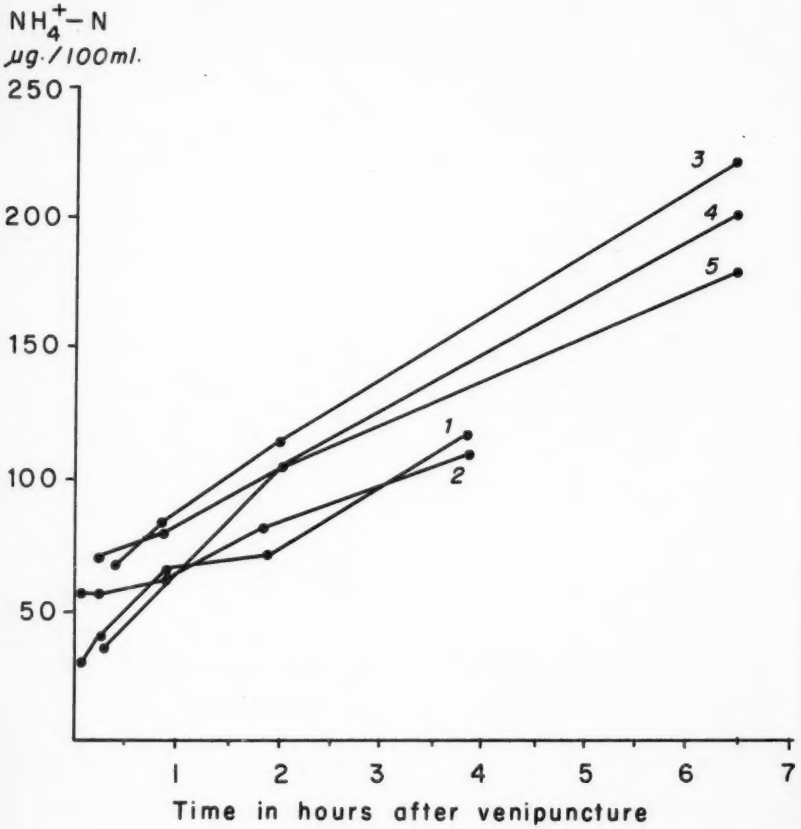

Fig. 2. Graph showing spontaneous rise in ammonium concentration in random samples of blood from five normal persons.

It is evident that the ammonium increased in all samples tested, and that the rate was different in each case. From these observations it might be concluded

that this source of error could be eliminated by starting the test immediately after venipuncture. Since this is not feasible, 20 minutes was arbitrarily selected as a suitable period. In this interval, the rise of ammonium is probably small. Twenty minutes does permit time to bring the specimen back to the laboratory and to prepare for the analysis.

Effect of alkalies on ammonia evolution. Seligson and Hirahara[3] reported that exposing blood to dry crystals of potassium carbonate not only caused the preformed ammonia to be liberated from ammonium compounds but also the hydrolysis of labile substances to yield additional ammonia. Presumably the hydrolysis was caused by an excessively high pH. They further reported that hydrolysis could be virtually eliminated by substituting a mixture of potassium carbonate and potassium bicarbonate crystals for potassium carbonate alone. This principle was applied to the Conway technic by employing as the alkalizing agent a solution of potassium carbonate and potassium bicarbonate saturated with respect to both chemicals.

Table 1 shows the pH values of various solutions and mixtures. These measurements were made with a Cambridge Micro condenser type glass electrode in conjunction with a Cambridge Research model pH meter.*

Table 1.—*The pH values of alkalies and blood-alkali mixtures*

Material	pH
Saturated potassium carbonate	13.1
Buffered alkali	10.5
Saturated potassium carbonate plus whole blood	11.5
Buffered alkali plus whole blood	99

Figure 3 compares the effects of the two alkalizing agents on blood from normal persons. The diffusion times were 10, 20, 40, and 60 minutes. Standards were run concurrently with each set of analyses. They were diffused for the same lengths of time. All analyses were performed at room temperature. Values of ammonium were calculated in each instance by reference to a standard exposed to the same alkalizing agent for the same length of time as the sample. The use of buffered alkali resulted in fairly consistent values of ammonium regardless of the diffusion period up to one hour. But when saturated carbonate was employed, continuously rising concentrations were obtained. These observations may be interpreted as indicating the hydrolysis of compounds in the sample to produce additional ammonium.

* *Cambridge Instrument Co.*

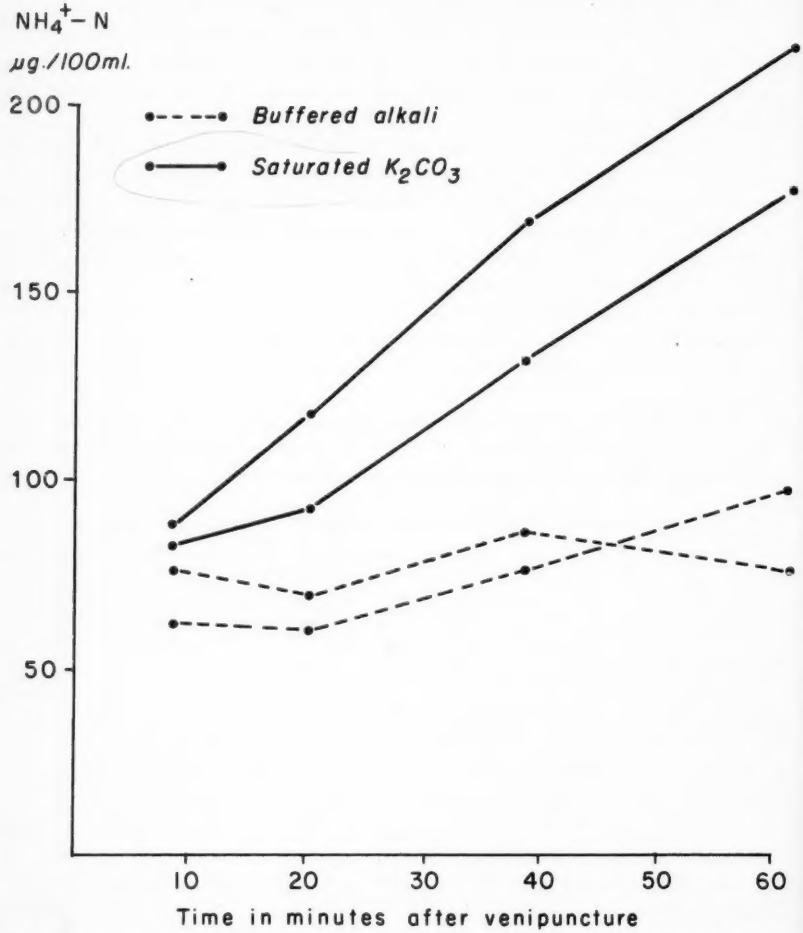

Fig. 3. Graph showing effect of alkalizing agents on ammonia evolution in two samples of normal blood.

Table 2 presents supplementary data that reinforce the conclusion implicit in *Figure 2,* namely that potassium carbonate causes the production of "extra" ammonium. The additional ammonium observed in some samples after 60 minutes' exposure to buffered alkali is attributed to the spontaneous production of ammonia that was occurring regardless of the presence or absence of any type of alkali.

Table 2.—*Effect of buffered alkali and saturated carbonate on blood ammonium in eight normal persons*

Sample number	NH_4^+-N in blood samples, μg./ 100 ml.					
	Tested with buffered alkali			Tested with saturated carbonate		
	20 min.	60 min.	Increase	20 min.	60 min.	Increase
1	69	67	—	115	203	88
2	177	174	—	174	322	148
3	58	41	—	97	152	55
4	63	64	1	98	168	70
5	77	91	14	95	179	84
6	116	143	27	171	214	43
7	53	84	31	80	160	80
8	93	144	51	170	218	48

Precision of the method. To test the reproducibility of the method, an ammonium sulfate solution containing 200 μg. of ammonium per 100 ml. was analyzed on different days over a period of one and one-half months. *Table 3* presents the data obtained.

The mean value for the 20 analyses was 206 μg. per 100 ml. with a standard deviation of 13.5 and a mean deviation of 6.0.

Recovery studies. An experiment to appraise the attainable accuracy of the method was performed. Ammonium sulfate was added in various quantities to three different blood samples as indicated in *Table 4.*

Normal blood ammonium values. The blood ammonium concentrations from 18 apparently healthy adult human beings were determined with this method. The range was from 36 to 75 μg. with a mean of 55 μg. per 100 ml. The standard deviation was 10. *Table 5* gives the values for each person in the series.

In contrast to values in normal individuals are those observed in patients in hepatic coma or in stupor as shown in *Table 6.*

Clinical Applications of the Method

In the past decade there has been great interest in the importance of ammonium intoxication in patients with hepatic coma. The ingestion of ammonium chloride is known to produce stupor and coma in cirrhotic patients,[7] and elevated blood ammonium concentrations in patients with gastrointestinal bleeding is almost pathognomonic of cirrhosis.[8]

Chalmers,[9,10] in an excellent review of the problem, points out that hepatic coma is a complicated derangement of metabolism in which prolonged elevations

Table 3.—*Values obtained on ammonium sulfate samples containing 200 μg. of NH_4^+-N per 100 ml.*

Sample	NH_4^+-N, μg./100 ml.
1	226
2	191
3	228
4	197
5	185
6	208
7	208
8	194
9	194
10	218
11	229
12	206
13	205
14	224
15	207
16	192
17	200
18	212
19	189
20	212

Table 4.—*Recoveries of ammonium added in the form of ammonium sulfate to three samples of blood*

Blood sample	NH_4^+-N, μg./100 ml.			Percentage of recovery of calculated total NH_4^+-N, per cent
	Initially	Added	Finally	
1	113	52	170	103
	113	80	202	105
	113	87	203	108
2	56	90	154	105
3	86	90	185	105

Table 5.—*Blood ammonium values from 18 normal persons*

Sample	NH_4^+-N, μg./100 ml.
1	45
2	45
3	64
4	36
5	54
6	54
7	45
8	68
9	56
10	66
11	52
12	75
13	50
14	49
15	69
16	53
17	48
18	74
Mean	55
S.D.	10

Table 6.—*Blood ammonium concentrations in three patients in coma and two in stupor*

Patient	Clinical condition	NH_4^+-N, μg./100 ml.
1	Coma	600
2	Coma	425
3	Coma	225
4	Stupor	294
5	Stupor	234

of blood ammonium may cause central nervous system symptoms, but frequently may be only one of many biochemical factors responsible for symptoms.

A reliably accurate determination of blood ammonium concentration is of great clinical value in the differential diagnosis of stupor and coma,[11] particularly in cases of unsuspected cirrhosis. In the management of patients in coma the blood ammonium concentration is a useful guide in treatment with intravenous arginine when hyperammonemia is present. As shown in *Figure 4*, adequate

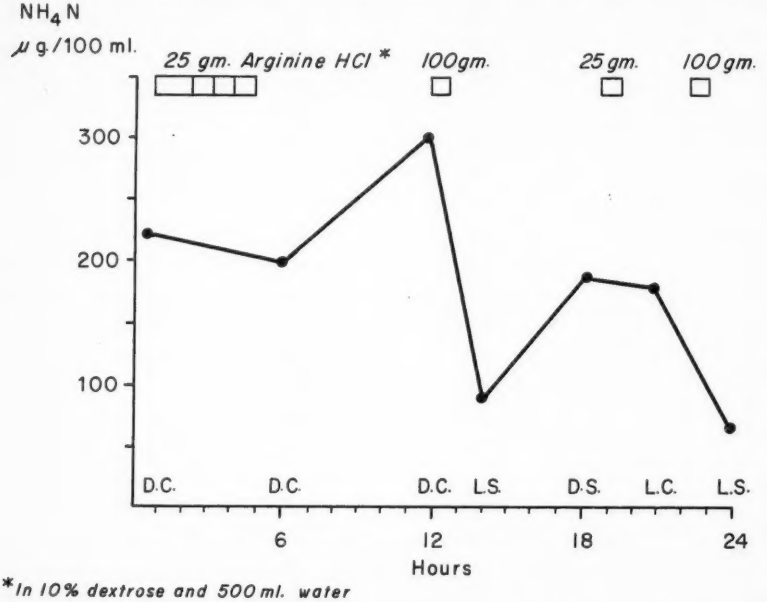

Fig. 4. Graph showing the effect of dosages of arginine intravenously injected, and infusion times on blood ammonium concentration and central nervous system symptoms in a patient with hepatic cirrhosis and gastrointestinal bleeding. Abbreviations are: L.S., light stupor (easily aroused); D.S., deep stupor (confused, disoriented); L.C., light coma (responsive to painful stimuli); D.C., deep coma (unresponsive to painful stimuli).

amounts of arginine resulted in significant lowering of ammonium concentrations in the blood. Although this response is not always followed by a rapid change in depth of coma, all measures are of value which will help to restore consciousness and an effective cough.

Serial blood assays after ingestion of 1.0 gm. of ammonium chloride have been of value in determining the patency of portacaval shunts *(Fig. 5)*.

Summary

A modification of the Conway technic for the determination of blood ammonium with a high degree of accuracy and reproducibility is presented. In this

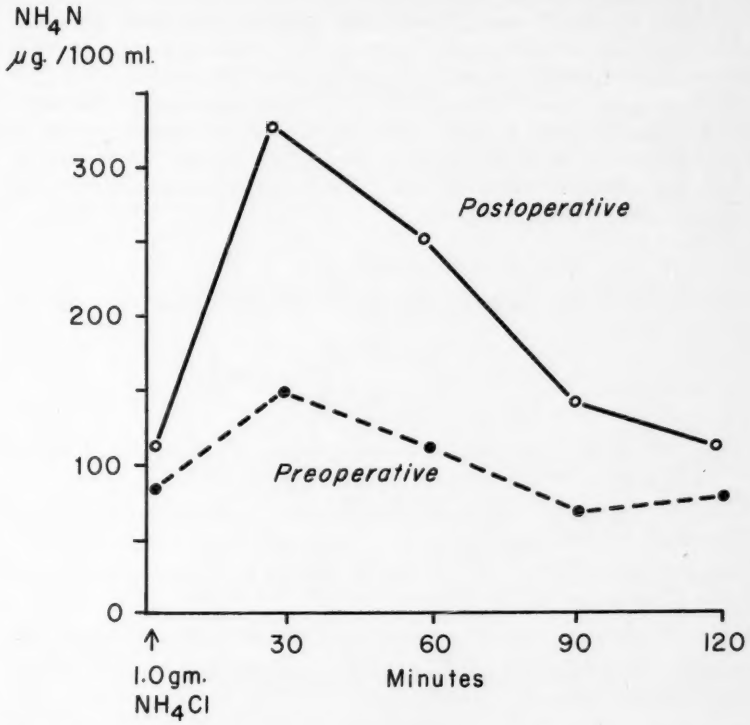

Fig. 5. Graph showing blood ammonium levels in one patient after ingestion of 1.0 gm. of NH_4Cl before and after portacaval shunt.

method the four chief sources of error have been eliminated or their effects have been minimized. These errors arise from such factors as the infinitesimally small quantities of ammonium present in blood, the spontaneous increase in concentration that occurs after venipuncture, the possibility of contamination during performance of the test and, finally, the danger of hydrolysis of labile ammonium-producing compounds in the blood by the use of excessively strong alkalizing agents.

The inherent difficulty in measuring the extremely small quantities of ammonium present in blood is lessened by carefully adjusting the concentrations and the relative quantities of reagents and by using a precise microburet for the titration. Errors arising through the spontaneous production of ammonia, although not susceptible to control, can be minimized by starting the test at a short but fixed time after venipuncture. Contamination of the specimen or of the glassware is virtually eliminated by keeping the sample in the syringe until time for analysis,

and by rinsing the unit thoroughly with absorbing fluid before starting the test. Alkaline hydrolysis of labile ammonium-producing compounds in the blood is largely prevented by using a buffered alkalizing agent.

The measurement of blood ammonium is of clinical significance in the differential diagnosis of unsuspected cirrhosis with central nervous system symptoms, in the evaluation of treatment of patients with arginine glutamate, in the determination of the patency of portacaval shunts, and in specialized studies involving the measurement of blood distribution.

Acknowledgment

The authors express sincere thanks to Mr. Robert P. Placko for technical assistance in this study.

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PERCUTANEOUS RETROGRADE CAROTID ARTERIOGRAPHY: A NEW TECHNIC

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Department of Neurological Surgery

ROENTGENOGRAPHIC demonstration of arteries in the neck, the chest, and the upper extremities is possible with a new technic *(Fig. 1)* that is safe, simple, and is easily performed.

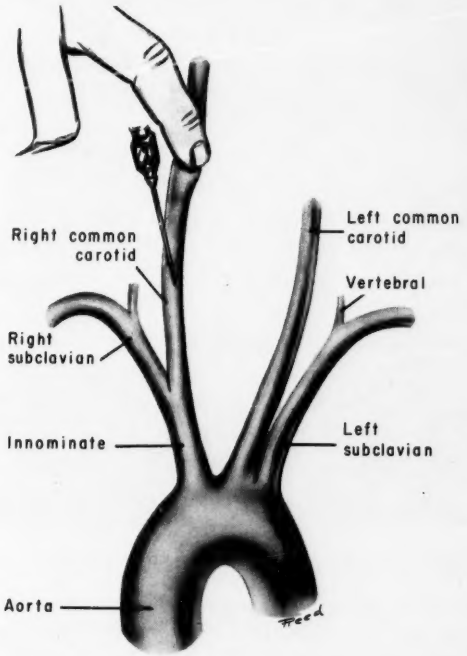

Fig. 1. Sketch showing the technic of retrograde injection of the common carotid arteries. In this case the right carotid artery is prepared for injection.

Initially we employed retrograde injections of the carotid arteries to visualize the origin of the carotid artery. We discovered that injection of the right carotid artery permitted visualization of the innominate, subclavian, vertebral, and brachial arteries, while injection of the left carotid artery permitted visualization not only of the carotid take-off, but also of the descending aorta and, occasionally, the left subclavian artery. The courses of these vessels could be conveniently studied.

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Retrograde injections were used in a series of 16 patients as an aid in diagnosing atherosclerotic lesions. No unfavorable side-effects were produced.

Technic

Endotracheal anesthesia was used in 14 patients, and local anesthesia with 1 per cent procaine hydrochloride, was used in 2 patients.

In the anesthetized patient, a No. 18 gauge needle is inserted percutaneously in the common carotid artery. Any technic for carotid artery puncture may be used for retrograde studies, but the needle should be inserted into the carotid artery pointing downward *(Fig. 2)*.

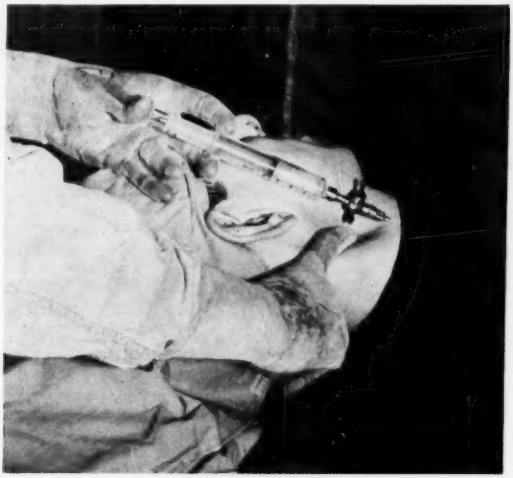

Fig. 2. Photograph showing retrograde injection of the right carotid artery.

The patient's chin should be slightly rotated to the side opposite injection, to give the operator accessibility to the distal common carotid artery for compression. Manual compression is applied to the artery above the needle puncture. Obstructing the cephalad flow permits more contrast medium to be sent toward the origin of the carotid artery.

For injections of the right carotid artery, a blood-pressure cuff should be placed on the right arm and should be inflated above the patient's systolic pressure. This will obstruct the brachial flow and will permit concentration of the contrast medium in the innominate and right vertebral arteries. For injections of the left carotid artery, occlusion of the left brachial artery is useless because of the direct aortic origin of the left common carotid artery.

For demonstration of either the right or left side the contrast medium is injected rapidly, and while the last milliliter is being injected a roentgenogram is made

(Fig. 3A and B). A rubber-lead shield is used to protect the operator's hands from radiation.

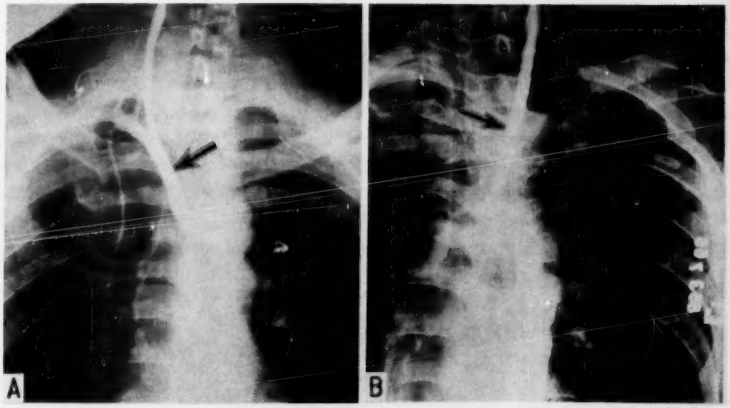

Fig. 3. A, Right retrograde carotid arteriogram showing common carotid, vertebral, subclavian arteries, and branches; the innominate artery is indicated by the arrow. B, Left retrograde carotid arteriogram showing the left common carotid artery (indicated by the arrow) and the descending aorta.

From 10 to 20 ml. of 50 per cent Hypaque* is adequate. Serial films may be started during mid-injection, but probably add little or no information to the single anteroposterior exposure centered over the sternal notch.

Arterial compression may not be necessary. Retrograde injections without compression were carried out in 3 of the 16 patients, because of thrombosis of the opposite internal carotid artery. Carotid take-offs were adequately demonstrated in two of those three patients.

Discussion

Formerly, retrograde injection of the right carotid artery was employed to visualize structures in the posterior fossa, via indirect filling of the right vertebral artery. This procedure was described by Moniz, Pinto, and Alves[1] and later modified by Elvidge.[2] No roentgenographic demonstration was given of the pathway of the contrast medium during the retrograde injection.

Retrograde injection of the left side apparently has not been previously described. Such an injection would rarely demonstrate the left vertebral artery, because the left carotid and left subclavian arteries arise separately from the aorta. The early investigators were interested not in atherosclerotic lesions, but in visualization of the posterior fossa, so did not pursue retrograde injections of the left carotid artery.

The great vessels of the neck may be outlined by direct aortic puncture,[3] or by retrograde arterial catheterization.[4] These are more formidable procedures than

**Hypaque sodium 50%, Winthrop Laboratories.*

percutaneous retrograde carotid arteriography.

Direct injection of the subclavian artery is not hazardous if the needle is directed medially, away from the apex of the lung.[5] The subclavian artery is less accessible than the carotid artery, and the injection of the left subclavian artery probably will not demonstrate the left carotid artery. If complete arterial visualization in the neck is desired, both a right and a left retrograde carotid and a left subclavian arteriogram are performed.

In performing a retrograde injection, it is technically more advantageous to direct the needle caudad than to direct it cephalad, as the carotid artery is more accessible for compression, and a more thorough and rapid injection of contrast medium is possible. As previously stated, a retrograde flow of contrast medium may be obtained without compression if the needle is directed downward.

Conclusion

Percutaneous retrograde carotid arteriography is a safe, useful, and simple adjunct to arterial investigation, and permits demonstration of the vessels proximal to injection.

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FIVE-YEAR CURE OF HEMIFACIAL SPASM

Report of a Case

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HEMIFACIAL spasm *(Fig. 1)* is a condition in which paroxysms of contractions affect the muscles supplied by the facial nerve. In a review of 106 cases, Ehni and Woltman[1] point out that the twitchings resemble those resulting from intermittent faradization of the nerve. The eyelids are almost always involved. The condition is usually unilateral and may occur during sleep. The patient feels no compulsion to make the movement and is unable to stop it. He cannot produce the twitchings voluntarily with anything like the speed with which they spontaneously occur. Voluntary movements may precipitate the spasms. The condition affects women more commonly than men and does not occur in children. Fourteen of Ehni and Woltman's[1] patients had impaired hearing on the affected side and three had tic douloureaux. Medical treatment was of no help. These authors reported no pathologic study in their own cases, but stated that such study by other investigators either disclosed nothing to account for the spasm or revealed gross progressive lesions such as tumors or aneurysms.

The analogy between hemifacial spasm and trigeminal neuralgia is obvious from the above account. Since intracranial neurolysis of the fifth nerve relieves the painful paroxysms of trigeminal neuralgia,[2] it seemed worthwhile to try a similar operation on the seventh nerve for the motor paroxysms of hemifacial spasm.

Report of a Case

A 36-year-old woman was examined in June, 1953, because of twitching of the left side of the face, which had increased steadily in severity for two years. The twitching consisted of bursts of clonic muscular spasms that were intermittent and limited strictly to the left side. Each paroxysm lasted from 10 to 20 seconds, usually starting at the angle of the mouth and spreading to the orbicularis oculi and all of the muscles supplied by the facial nerve. Each paroxysm was followed by a refractory period of 10 seconds or longer. The twitching of the facial muscles was precipitated by movements of the face particularly in talking and in eating, but also occurred at rest. She was free of the twitching for as long as four hours. There had been progressive impairment of hearing in the left ear for 12 years (since 1941). There was no associated tinnitus. For the preceding year she was subject to attacks of vertigo and nausea which were apt to occur when she started to eat.

On examination the patient exhibited typical paroxysms of left hemifacial spasm involving all muscles supplied by the facial nerve. Between attacks there appeared to be slight weakness of the lower facial muscles. There was no impairment of sense of taste. Audiometric studies disclosed total deafness in the left ear and mild mixed deafness in the right ear. Caloric stimulation with 1 ml. of ice water elicited no vestibular response on either side. Roentgenograms of the skull were negative. The cerebrospinal fluid pressure was normal. The clinical impression was a lesion in the left cerebello-

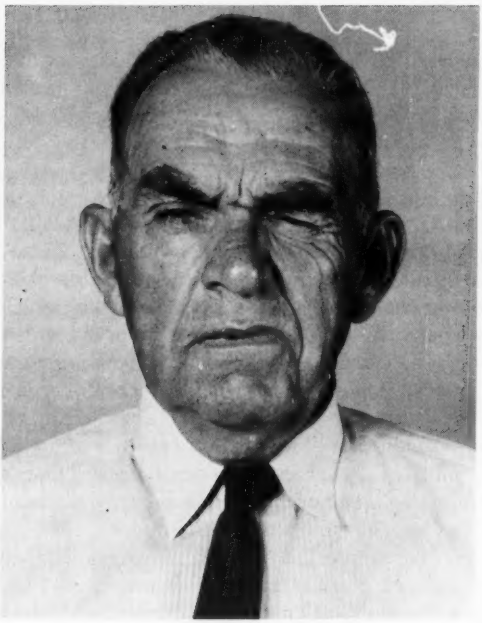

Fig. 1. Photograph of a patient with typical hemifacial spasm.

pontine angle causing hemifacial spasm and deafness. Banthine* taken orally and vitamin B_{12} administered intramuscularly afforded her no relief.

The patient was re-examined two years later, at which time the condition was unchanged except that caloric stimulation produced slight but definite responses in each ear. Because of increasing experience with the effectiveness of neurolysis in the treatment of trigeminal neuralgia, a surgical exposure of the seventh nerve was advised.

On July 25, 1955, with the patient in the sitting position, a right suboccipital craniotomy was performed and the cerebellar lobe was retracted from the posterior surface of the petrous bone. A loop of the internal auditory artery lay against the posterior surface of the eighth nerve. The arachnoid of the pontine cistern was opened and the artery was dissected free of the nerve. The portion of the seventh nerve that could be seen appeared normal. The seventh and eighth nerves were gently manipulated with a nerve hook introduced into the porus acusticus internus. A piece of Gelfoam then was placed beneath the artery to separate it from the eighth nerve, and the operation was concluded.

For 24 hours after operation facial twitching was absent and there was no weakness of the facial muscles. Hemifacial spasm then recurred, but it was much milder and less frequent than before operation. Six months postoperatively the hemifacial spasm con-

*Banthine Bromide, methantheline bromide, U. S. P. (β-diethylaminoethyl xanthene-9-carboxylate methobromide), G. D. Searle & Co.

sisted of occasional, slight, fibrillary tremors of the orbicularis oculi and occasionally a slight twitching of the angle of the mouth. There had been no further attacks of vertigo. The hearing loss was unchanged. Five years postoperatively (1960), the patient reported only the rare occurrence of a barely detectable tremor of the lower eyelid.

Summary

In a patient with hemifacial spasm the seventh nerve was treated by an intracranial neurolysis similar to that employed on the fifth nerve for the relief of trigeminal neuralgia. The spasm rapidly diminished after operation, and five years later the patient was without symptoms except for a rare slight tremor of the lower eyelid.

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RADIOTHERAPY IN THE TREATMENT OF CARCINOMA OF THE URINARY BLADDER

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MALIGNANT tumors of the urinary bladder arise from transitional epithelium and may be expected to respond well to ionizing radiation, but this favorable response has not occurred in the past. Tumor doses with 250-kv. apparatus were necessarily inadequate and only the most advanced lesions were treated. Currently the availability of high-energy, skin-sparing sources of radiation makes it possible to deliver cancerocidal doses to the tumor volume; therapeutic technics and skill are minimizing or preventing the types of sequelae formerly encountered; and more lesions are now being treated in the early stages by radiation as the effectiveness of some surgical procedures is being challenged. An attempt will be made to review the events that have led some clinicians to reassess the position of radiotherapy in the treatment of carcinoma of the urinary bladder.

Classification of Tumors and Prognosis

Survival of patients who had undergone surgical treatment for carcinoma of the bladder was evaluated in terms of various therapeutic technics in the early years. Later some investigators began to assess survival on the basis of histologic findings. However, despite improvements in operative management, patients with ostensibly localized lesions of a favorable histologic type were dying of recurrent cancer of the bladder. It remained for Jewett[1] to establish the validity of survival as a function of invasion of the muscularis. He proved conclusively that the stage (extent of tumor) and to a lesser degree the grade (cellular dedifferentiation) were the most significant prognostic indexes. This classification brought into sharper focus the limitations of cystoscopic findings. It led to the development and refinement of transurethral instruments capable of providing the pathologist with tissue more representative of the actual extent of the tumor. It re-emphasized the value of the often forgotten principles of physical examination. In essence, Jewett[1] shored up urologic practice in this special field by classifying tumors of the bladder according to the depth of invasion. He concluded by saying that in most instances the prognosis and a suitable surgical attack could be planned on the basis of cystoscopic findings, bimanual examination, and an adequate histologic search for invasion. *Figure 1* is Marshall's modification of Jewett's[1] original classification as it appears in Milner's[2] report.

Baker,[3] in a further attempt to assess operability for cure, investigated the intravesical lymphatic network. This is circumferential and crosses the midline anteriorly and posteriorly. Experimental work suggested the relationship between the invasion of the muscle and lymphatic involvement. When the muscle was invaded for more than 50 per cent of its depth, involvement of the vesical as well as extra-

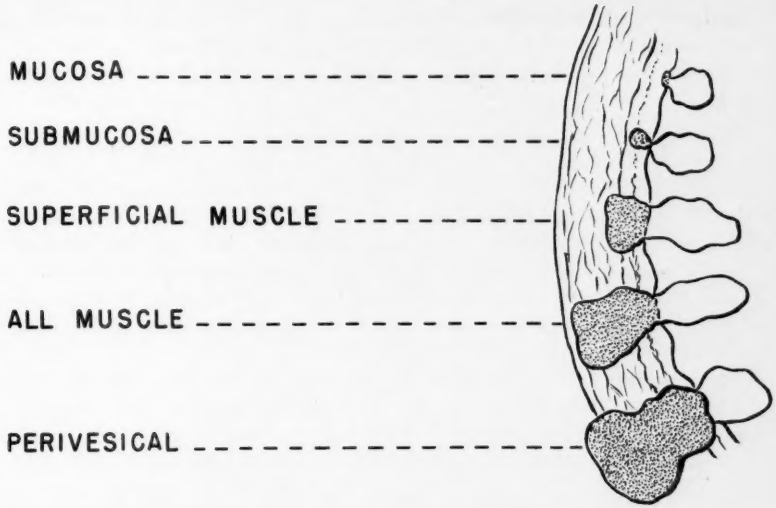

Fig. 1. Marshall's modification of Jewett's original classification of tumors of the bladder. (Courtesy of Milner, W. A.: Role of conservative surgery in treatment of bladder tumours. Brit. J. Urol. 26: 375-384, Dec. 1954; and the British Journal of Urology, Edinburgh and London.)

vesical lymphatics occurred. This prompted Baker[3] to question the value of some radical surgical procedures.

Surgical Treatment

The study by Baker,[3] and earlier summations by Brice, Marshall, Green, and Whitmore,[4] and Higgins[5] indicate a trend toward conservative treatment as far as statistics for operative mortality and five-year survivals in advanced carcinoma of the bladder are compared. The established role for surgery in small, superficial lesions has been summarized by Nichols and Marshall[6] and needs no repetition here. Riches[7] reported a five-year survival rate of 35 per cent among 85 patients undergoing partial cystectomy for carcinoma, and of 16 per cent among 100 patients subjected to total cystectomy. Marshall, Holden, and Ma[8] reported a 53 per cent five-year survival rate of 123 patients who had undergone partial cystectomy, and 21.2 per cent surviving at five years of 56 patients who had undergone total cystectomy. In each of these series[7,8] there were no patients surviving who had involvement of pelvic lymph nodes; the operative mortality ranged from 12 to 18 per cent. Whether more radical procedures such as total cystectomy combined with regional lymphadenenectomy as advocated by Leadbetter, according to Baker,[3] will improve survival or add to palliation remains to be developed.

Technically, success or failure in radical surgery for carcinoma of the bladder is almost entirely contingent on the prior integrity of the upper urinary tract and

the urinary diversionary method chosen. There are no known survivors among those patients with preoperative evidence of urinary tract obstruction. Certainly other factors such as location of the tumor and previous treatment must be considered.

Radiotherapy

Radiation by various technics has been utilized in the management of cancer of the bladder. Radon seed implants, interstitial radium needles, intracavitary insertion of radium or cobalt sources, tantalum- or cobalt-wire implants, and external roentgen sources have been tried with a wide range of success by individual cancer therapists. Each technic makes a contribution. The ultimate choice will depend on the extent of the tumor, and to a lesser degree on its histologic characteristics.

The urologist uses radon implants *(Fig. 2A)* usually transurethrally and occasionally suprapubically. This method requires that the tumor be localized and superficially invasive, and that provision for adequate bladder drainage has been established. Others have implanted radium element needles interstitially *(Fig. 2B)*; this method requires two operative procedures and is seldom used now.

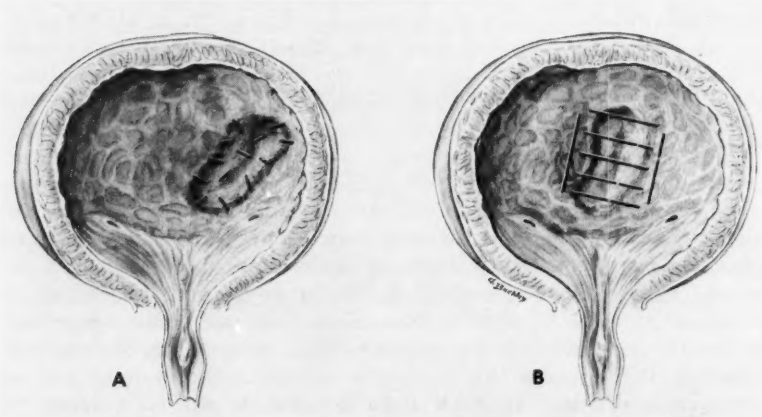

Fig. 2. A, sketch showing radon seed implant. B, sketch showing radium needle implant.

Both methods require a basic knowledge of radiation dosimetry to insure a homogeneous distribution of the radioactive sources throughout the tumor volume. These local radiation implants are always preceded by resection and fulguration.

Intracavitary radioactive sources have been used with notable success by Friedman and Lewis[9]. Accurate placement of the sources is essential, and only superficial lesions can be effectively treated. This technic may be useful in cases of multiple superficial papillomata when cystectomy cannot be performed *(Fig. 3)*.

Fig. 3. Sketch showing intracavitary method using radium or Co-60 as the source.

External roentgen therapy theoretically would seem to be more promising than the above-mentioned technics. Almost any tumor volume can be included and more homogeneous doses can be delivered. The energy of the primary beam will per se constitute the only physical limitation in increasing the percentage tumor dose. Conventional or orthovoltage methods have a narrow usefulness as the maximum tumor exposure dose can rarely exceed 2500 to 3000 r in four weeks without excessive injury to the integument and to deeper pelvic structures. Even considering the refinement of multiple portal and rotational technics, tumor doses in the cancerocidal range are not attained. Palliation in isolated cases is the best result to be expected.

Sources operating at energies from 2 Mev. to 50 Mev. are currently available in large medical centers keyed to a vigorous program of cancer research and treatment. All these sources produce ionizing radiation that is skin sparing, greater in penetration, and more geometrically pure in its transmission through the body than conventional radiation. Attention to clinical detail and tissue response cannot be neglected. There is no inherent magic associated with these higher energies in terms of five-year survival. The biologic intangibles involved as radiation interacts with matter, parallel earlier radiation experience. Time-dose relationships, selective tissue destruction, and careful follow-up studies are all important factors in radiotherapy. Greater expectations, however, may now be nurtured as independent investigators have the opportunity to treat and to follow comparable groups of patients. The best results will be obtained through closer liaison than has existed heretofore among the urologist, the radiation therapist, and the pathologist.

Tumor exposure doses of 6000 to 8000 r can be delivered in treatment times of from six to eight weeks. The daily tumor exposure dose should rarely exceed 200 r. This dosage assumes that the lesions are potentially curable. When palliation is the best that can be expected, then exposure doses of from 3000 to 4500 r are given in treatment times of from three to four weeks. These figures are an ideal and cannot always be attained as patients vary in their tolerance to treatment. The radiation has to be individualized rather than standardized. The use of multiple portals of entry seems preferable to the use of opposing fields *(Fig.4)*.

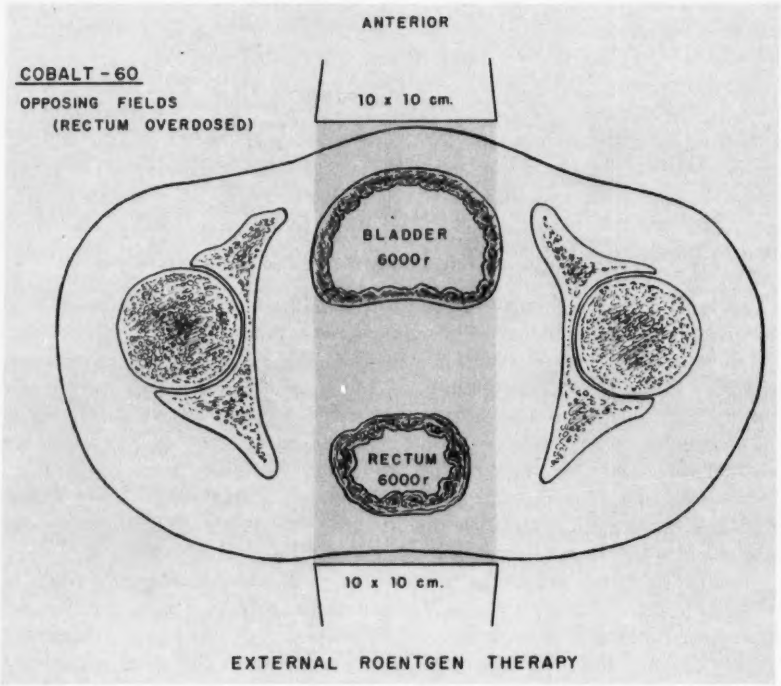

Fig. 4. Sketch showing estimated percentage depth dose of Co-60, 80 cm. target skin distance (TSD); half-value layer (hvlayer) 10.5 mm. Pb.

In our practice we employ a single anterior and two posterior oblique (8 by 10 cm. or 10 by 10 cm.) fields *(Fig. 5)*. In this way greater doses can be delivered to the tumor volume without overtreating the rectum. Rotation added to supervoltage radiation is the ultimate in precision multiple small-beam therapy as advocated by Trump and associates[10], and Browne and Ogden[11]. Both technics need careful pretreatment assessment of the tumor mass, mapping of isodoses, and roentgen confirmation of the treatment fields.

High energy sources are to be preferred whether for palliative or curative therapy. The comfort experienced by the patients far exceeds other considerations. We use the Picker cobalt-60* teletherapy unit with the Johns-MacKay collimating system. The unit contains a 4620-curie source that delivers 100 r per minute at a treatment distance of 80 cm.

Pretreatment assessment. Almost any neoplasm of the bladder with the exception of papillomas should be given a trial of radiation inasmuch as the morbidity in untreated vesical cancer is high. Those that most certainly should be treated by radiation include lesions that are not curable by surgical means, usually classified as stages C or D; infiltrating tumors that recur after resection; and in some isolated

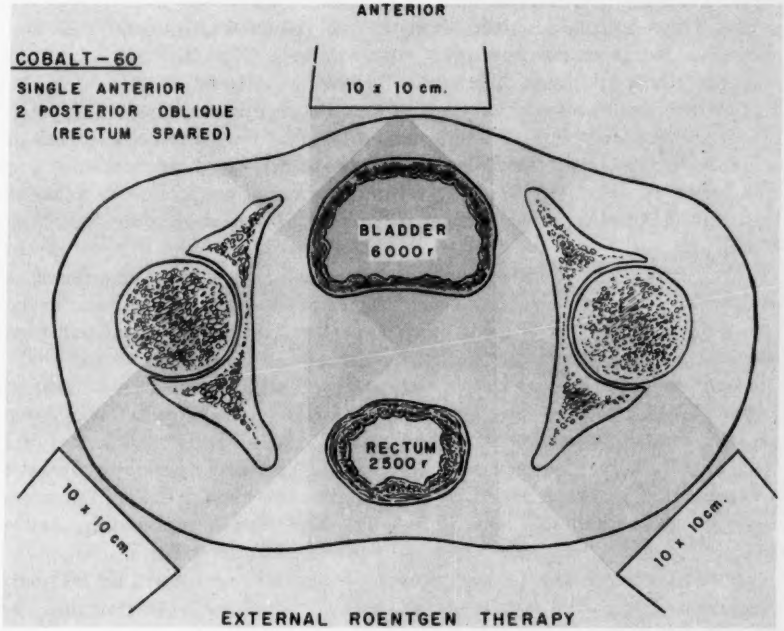

Fig. 5. Sketch showing estimated percentage depth dose of Co-60, 80 cm. TSD; hvlayer 10.5 mm. Pb.

instances, tumors extending beyond the line of excision or for which there is histologic proof of vascular invasion.

In advanced lesions (where urinary tract obstruction exists or there is good evidence of perivesical extension of lymphatic metastasis), therapy can only be expected to be palliative in intent. The aim here is to give symptomatic relief and to reduce hemorrhage. This can be accomplished by delivering 3000 to

**The radioactive cobalt was obtained on authorization of the Isotopes Division, the United States Atomic Energy Commission, Oak Ridge, Tennessee.*

4500 r in from three to four weeks, with little discomfort to the patient.

In invasive lesions not suitable for a definitive surgical approach but without extravesical extension, the radiotherapist may assume a more optimistic attitude. Recent reports by Poole-Wilson[12], Cuccia, Jones, and Crigler[13], and Browne and Ogden[11] buttress such thinking. These reviews plus re-evaluation of unfavorable results in surgical treatment suggest that more can be accomplished when joint consultation between the surgeon and the radiotherapist replaces unilateral decisions in cancer therapy. An attempt is made to treat some of these patients radically in an all-out effort to control the primary lesion. While 8000 r can be delivered to the bladder the margin of safety is small, and therefore the average maximum tumor exposure dose is from 5000 to 6000 r in from five to six weeks. Three fields as described above are used. Each field is treated daily and the summated depth exposure dose is 200 r or less. Every attempt is made to minimize the rectal insult. Admittedly this course will not always be feasible, because other factors may delimit the total tumor dose. Previous infection, a reduced bladder capacity, and lesions arising near the vesical neck may be deterrents to intensive therapy. Poor renal function, while in itself not a contraindication to major therapy, may lead to complications requiring interruption of planned treatment. Urinary diversion occasionally may be necessary before the beginning of radiation.

The tumor dose is calculated according to established dosimetry and the fields are checked by exposing industrial roentgen film to the cobalt-60 beam in the treatment position. The patients are followed by the urologist and radiation therapist during and after the treatment course.

Radiation sequelae. Ionizing radiation produces peculiar changes in the mucosa of the bladder which require many months and oftentimes a year to heal completely. Evaluation of response to radiation then may not be possible for some time after therapy. Acute changes occur during the third and fourth weeks of treatment and are characterized by frequency, urgency, and dysuria. Cystoscopic findings include bullous edema and a generalized exudative mucositis. As the reaction subsides, edema may persist and mucosal pallor and telangiectasia appear.

Severe chronic changes may supervene, heralded by hematuria, urgency, and frequency. The cystoscope discloses interstitial fibrosis, localized ulceration, and massive telangiectatic areas. These findings are clinically significant and, while unavoidable in some cases, they may be a necessary consequence in the radical radiation treatment of otherwise inoperable cancer of the bladder. This is not to say that the therapist in his attempt to achieve long-term survival will not heed symptoms that may be prodromal in character. It may be mandatory to interrupt treatment or to reduce the daily tumor dose in some instances.

Comparison of results. Cuccia, Jones, and Crigler[13] reviewed 100 consecutive cases of cancer of the bladder classified according to Marshall (cited by Milner[2]) and all with histologic confirmation. Cobalt-60 and the betatron were used to deliver tumor exposure doses from 5000 to 6000 r in from five to six weeks as

radical therapy. Palliative treatment consisted in delivering from 3500 to 4500 r in from three to four weeks. One anterior and two posterior fields were used. Of the 64 patients treated radically with radiation, 16 are living and well at two years and 15 of these are apparently free of cancer; 18 are symptom-free at one year and 16 of these are known to be free of cancer; and 14 patients are alive and well less than one year after treatment and 13 are free of tumor. Thirty-six patients received palliative radiation only and eight are living at one year. Complications were distressing in those patients receiving intensive treatment. Eleven patients had minor sequelae. Eighteen patients, however, experienced major reactions; 11 had rectal or vesical hemorrhage; 10 had a contracted bladder; 3 had bladder ulceration. Two of these 18 patients died of uncontrollable rectal bleeding. It is to be noted that each of the three patients with bladder ulceration had radiation therapy previously, and six of the patients with a reduced bladder capacity had undergone surgery previously. Perhaps severe radiation injury may be obviated by a more judicious use of radiotherapy.

Browne and Ogden[11] reviewed the records of 55 patients with histologically proved bladder carcinoma treated with rotational cobalt-60 teletherapy with or without previous surgery between December 15, 1954, and January 1, 1958, and a similar group of 45 patients treated surgically only. All cases were classified in accordance with Jewett's[1] grouping. Of the 55 patients treated with radiation, 47 received tumor exposure doses of from 5000 to 6000 r and eight patients received less than 5000 r. Five of the 55 patients were considered to have operable cancer but received only radiation; all five are living from one and one-half to four years after treatment. Thirty-six patients received radiation postoperatively. Eighteen of the 36 were treated for residual disease within two months postoperatively; 9 of these were living and well from one and one-half to three years after treatment. Eighteen of the 36 were treated for local recurrence more than two months postoperatively; five of these were living and well from one and one-half to three years after treatment. Fourteen of the 55 patients were considered to have inoperable cancer at surgical exploration; two of these were living with disease at one and one-half and two and one-half years after radiotherapy. Clinically, all patients having stages A or B1 lesions were alive and well at the time of the report; 62 per cent of those with stage C lesions were living without evidence of carcinoma; and 14 per cent of those considered inoperable were living but had persisting disease.

Forty-five patients were treated surgically. Thirty-nine patients were classified as having lesions of stage A or B and 28 (72 per cent) of these were alive and well; eleven had died of carcinoma; six patients who had cancer of stage C or D died of their disease.

Fifty-one per cent of all patients receiving radiation experienced minor complications, consisting of diarrhea and cystitis, during the third week of therapy. In five patients severe reactions developed; of the three who had hemorrhagic cystitis, two had been treated previously with radon implants. In two patients intractable

diarrhea developed. One patient with bladder hemorrhage underwent a total cystectomy for relief of symptoms.

Jewett,[1] and Marshall (cited by Milner[2]) by their classification made possible a more realistic clinical assessment of bladder cancer. Transurethral resection and fulguration with or without a radon implant would seem the treatment of choice for lesions staged[2] as O, A, or B. For lesions classified as B2, C, or D, recent experience indicates that well-planned radical radiotherapy may yield superior results.

Summary

The role of ionizing radiation as a definitive procedure in the treatment of carcinoma of the urinary bladder is reviewed. External gamma-ray therapy with cobalt-60 or alternate high-energy sources may offer more palliation to a greater number of patients than will the other radiation modalities. Careful treatment schemata co-ordinated with urologic and pathologic findings are essential to success. Radical radiation is effective in the control of some bladder carcinomas, and may proffer symptomatic relief in others. Preliminary reports from two independent medical centers suggest that radiotherapy can sometimes control inoperable cancer of the urinary bladder and can prolong survival in other cases. If other tumor centers would report on comparable programs it would serve to advance knowledge and skill in the use of radiation in the management of carcinoma of the urinary bladder.

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DEMONSTRATION OF COLLOIDOSMOTIC EFFECT OF BLOOD ON CEREBROSPINAL FLUID

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WHEN a hydrocephalic baby dies, the fall of pressure in the vascular tree is accompanied by immediate relief of tension at the fontanelle. Subsequently there occurs progressive retraction at the fontanelle, indicating reduction in volume of the intracranial contents. We have assumed that this is due to a reduction in volume of cerebrospinal fluid occasioned by its reabsorption into the blood; and that this occurs because the cessation of filtration pressure stops the formation of cerebrospinal fluid and permits the colloidosmotic pressure of the blood plasma to draw the fluid back into the blood compartment not only via the venous but also the arterial side of the capillary system.

In order to test the hypothesis we performed experiments with samples of blood and cerebrospinal fluid from four patients. From 2 to 4 ml. of heparinized blood was placed in a small cellophane sac. This was attached to a calibrated 2-ml. pipet and suspended in a 100-ml. glass cylinder containing cerebrospinal fluid removed from the same patient at pneumoencephalography. Cellophane (regenerated cellulose) is a comparatively good substitute for the capillary wall. It is not permeable to albumin, but it is permeable to water, electrolytes, urea, and other materials having molecules smaller than albumin *(Fig. 1)*. Care was taken that the hydrostatic pressure of the blood in the sac was always slightly higher than that of the surrounding fluid. This was accomplished by moving the pipet up or down so that the level of the blood was just 1 cm. above the level of the cerebrospinal fluid. Any change in volume of the blood in the cellophane sac and pipet could be accurately read.

In all four experiments there was a continuous increase in volume of the blood, indicating that water from the cerebrospinal fluid was entering the blood compartment. *Figure 2* is a composite graph of the increase in volume of the blood.

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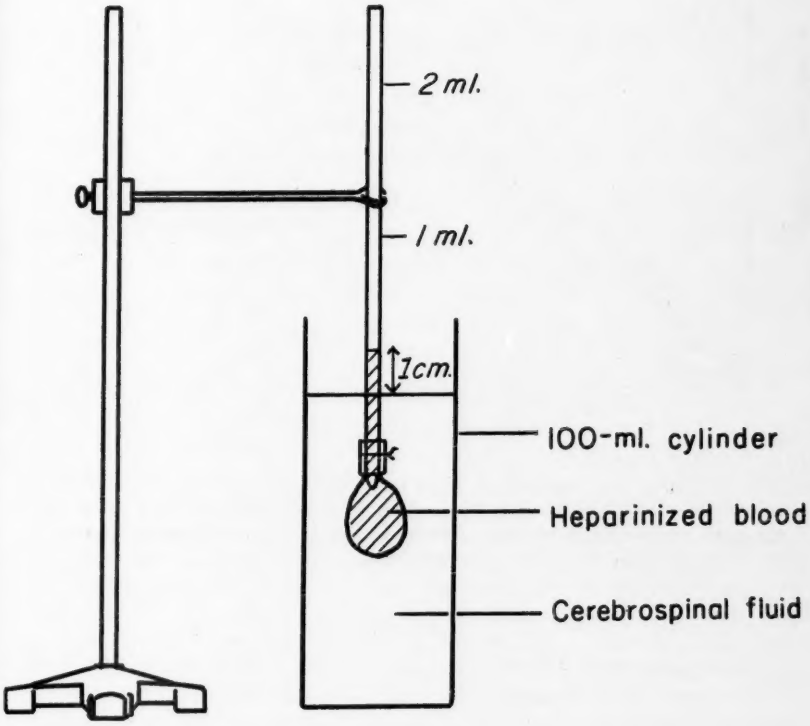

Fig. 1. Diagram showing how the increase of volume of blood in a cellophane sac suspended in cerebrospinal fluid is measured. To insure uniform distention of the sac, the height of the pipet is adjusted at each reading so that the level of the blood is 1 cm. above the level of the cerebrospinal fluid.

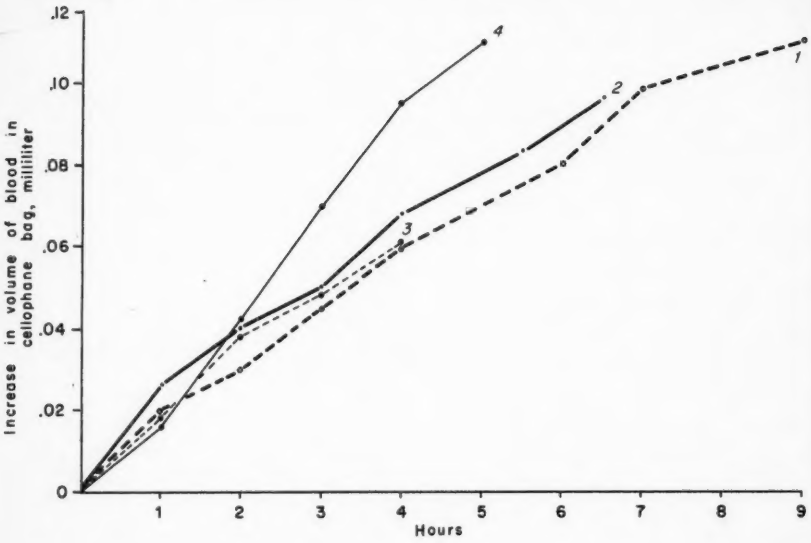

Fig. 2. Composite graph of results of four experiments, showing the volume increase with time of 2 to 4 cm. of blood suspended in cerebrospinal fluid at room temperature. Cellophane sacs each had a surface area of approximately 7.0 square centimeters. Hydrostatic pressure of the blood was maintained 1 cm. higher than that of the cerebrospinal fluid.

Conclusion

The size and shape of the cerebrospinal fluid spaces are not the same in death as they are during life, because colloidosmotic pressure, no longer counteracted by intracapillary pressure on either the arterial or the venous side, causes reabsorption of cerebrospinal fluid into the blood compartment.

GASTRIC CARCINOMA: REPORT OF TWELVE PATIENTS SURVIVING LONGER THAN FIFTEEN YEARS

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IN the past 30 years a decrease in the incidence of gastric cancer has been noted in the United States.[1,2] At the Cleveland Clinic in 1948, 135 new cases were diagnosed, while in 1958 there were only 70 new cases. Further evidence to support a true decrease in the incidence of this disease is obtained from the numbers of cases of gastric carcinoma diagnosed per thousand new patients. In 1942, 4.8, in 1948, 4.5, in 1950, 3.2, in 1955, 2.7, and in 1958, 2.7 new diagnoses of gastric carcinoma were made per thousand new patients at the Cleveland Clinic. Along with this steady decrease in incidence has been a striking increase in years of survival of patients who underwent surgery for gastric carcinoma. Hoerr[3] stated that in a personal series, 30 of 83 patients (36 per cent) surviving resection for cure were alive and free of disease five years or longer after resection. However, long-term survival after surgical treatment is rare. In 1959, Lubash and Cardillo[4] reported the case of a patient who survived 15 years and stated that they were able to find only four such reports in the English literature.

Although extensive clinical and autopsy studies have been done on patients who died from the disease, few studies have been reported of patients who survived. Because thorough clinical study can provide a sound basis for accurate prognosis and effective treatment, we recently analyzed records of 58 patients who survived five years or longer after surgery for gastric carcinoma.[5] In this series neither age of the patient nor duration of symptoms appeared to be related to survival. In no patient was there preoperative evidence of distant metastasis; and the presence of an abdominal mass in eight patients and of hepatomegaly in three patients neither contraindicated surgery nor precluded survival. In the group of patients with noninfiltrating lesions (27 patients with ulcerating tumors, 15 with polypoid tumors, and 9 with combined polypoid and ulcerative neoplasms), prognosis was more favorable in regard to long-term survival than in the group of 7 patients with infiltrating lesions. Local extension of the neoplasm to the serosa had occurred in 4 patients, and to adjacent organs in 12, including 1 patient with neoplastic extension to the right lobe of the liver. Seventeen patients of the total number in the study had metastatic involvement of the local lymph nodes.

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Because of the apparent infrequency of long-term survival from gastric carcinoma (Lubash and Cardillo[4]) we believe this report of 12 long-term survivors to be of interest.

Clinical Findings

Twelve patients, who survived 15 years or longer following surgery for gastric cancer, were studied. Two patients died of "heart attacks," 16 and 18 years after operation, while one patient is alive after 15 years, four after 16 years, two after 17 years, and three patients are living 18 years after operation. At the time of operation, five patients were in their fourth and five in their fifth decades. Recurrence of gastric carcinoma or development of other cancers might be expected in this age group, particularly since there already had been a host susceptibility to cancer. In this group no recurrence was observed, but a new primary gastric carcinoma developed in one patient eight years after his first operation. He survived 18 years after the operation for the first gastric carcinoma and 10 years after his second operation. The low incidence of occurrence of other carcinomas suggests that "a biological resistance" to cancer may develop.

In the present group the duration of symptoms before operation was more than one year in two thirds of our patients; only four patients had symptoms for less than one year. Therefore, a long duration of symptoms prior to operation does not preclude long-term survival. The earliest symptom was epigastric pain in eight patients, which was constant in six, and intermittent in the other two patients. Vomiting occurred in three patients and gastrointestinal bleeding in one patient. One patient was treated for pernicious anemia for one year before gastric carcinoma was diagnosed. Considerable weight loss with malnutrition occurred in six patients.

On physical examination none of the 12 patients had evidence of distant metastasis. Hepatomegaly, rectovesical shelf, or palpable nodes were not found. An epigastric mass was palpable in two patients and was questionable in two others. The presence of an abdominal mass is not necessarily a contraindication to an operation for cure.

Anemia was a frequent finding; seven patients had concentrations of hemoglobin of less than 8 gm. per 100 ml. and required preoperative transfusions of blood.

Of 11 roentgen examinations of the stomach, positive diagnoses of carcinoma were made in 10 patients, and a questionably positive diagnosis was made in one patient.

Operative Findings

The location of the neoplasm is of considerable prognostic importance. Since neoplasm of the pylorus usually causes obstruction, an early diagnosis is frequently possible. Tumors involving the distal third of the stomach are relatively easy to

resect. Of our 12 patients, carcinoma was found in the antrum in six, in the pars media in five, in both the antrum and the pars media in one.

According to Borrmann's classification,[6] tumors were grouped as follows: infiltrating lesions, three; polypoid lesions, four; polypoid-and-ulcerating lesions, three; and ulcerating lesions, two. Polypoid, polypoid-and-ulcerating, and ulcerating lesions offer a prognosis better than that of diffusely infiltrating neoplasms.

The presence of enlarged regional lymph nodes is not indicative of metastasis. One of us (C. H. B.) and Kane[7] previously reported that in two patients with carcinoma of the stomach, the lesions were considered grossly nonresectable for cure because of a large omental node present in each of them. Upon microscopic examination of the permanently fixed section of the omental node no evidence of tumor was found. Enlarged lymph nodes may be inflammatory rather than neoplastic. For this reason the presence of regional or distant metastasis should be proved by microscopic examination of frozen sections before the lesion is considered nonresectable for cure. Metastasis in the regional lymph nodes does not preclude a cure when an adequate excision can be accomplished. In this group of 15-year survivors, five patients had evidence of regional lymph-node metastasis.

Extension of the neoplasm to the gastric serosa or beyond the serosa is not a contraindication to the excision of the lesion when technically possible. Four patients had such extension of carcinoma; two to the serosa, one to the right lobe of the liver, and one to the lesser omentum.

Histologic Types of Carcinoma

The carcinomas in the 12 patients were histologically classified as follows: eight, adenocarcinoma; two, adenocarcinoma with mucin; and one each of infiltrating carcinoma simplex with mucin (colloid), superficial carcinoma simplex, and superficial carcinoma solid and simplex. In one patient two carcinomas of the stomach developed, accounting for 13 lesions in 12 patients. Compared with 100 consecutive patients operated on at the Cleveland Clinic Hospital for carcinoma of the stomach and studied by Fisher and Hoerr,[8] who found adenocarcinoma present in 21 per cent, patients with adenocarcinoma have a greater chance of survival and a better prognosis.

Illustrative Case Report

A 57-year-old man was first examined in April, 1941, because of indigestion and ulcer-like distress of four months' duration, and a 23-pound loss in weight. Roentgen examination revealed a filling defect in the prepyloric region. At operation an irregular mass was found in the pyloric area on the posterosuperior wall of the stomach, and an omental node 2 cm. in diameter. A hemigastric resection was performed with excision of a large part of the gastrocolic omentum, transverse mesocolon, and greater omentum. Histopathologic examination showed the lesion to be of the mucinous-and-colloid type with a small portion of the adenocarcinoma type. Section of four greater omental

nodes showed metastatic involvement in each node. The line of resection was free of tumor.

The patient was examined at frequent intervals. In April, 1946, a roentgenogram of the stomach revealed no evidence of neoplastic recurrence. In July, 1949, at the age of 65 years, he returned because of ulcer-like distress and loss of 25 pounds in weight during six months. A roentgenogram revealed a filling defect in the region of the lower esophagus and fundus of the stomach. A second operation was performed and a firm fungating mass was found to encircle completely the cardioesophageal opening. The remainder of the stomach was removed and an esophagojejunostomy was performed with splenectomy. Histopathologic examination showed an adenocarcinoma without mucin, different histologically from the one removed in 1941, with extension into the muscularis.

In December, 1952, roentgen examination revealed a normally functioning esophagojejunostomy; there was no evidence of recurrence of the neoplasm. In April, 1958, he reported being in satisfactory health. In the summer of 1959, at the age of 75 years, the patient died suddenly of a heart attack.

This patient had two primary gastric carcinomas of different histologic types; the second primary carcinoma was diagnosed eight years after the first. The patient survived 18 years after excision of the first cancer and 10 years after excision of the second. At the time of his death there was no clinical evidence of recurrence or metastasis.

Comment

In contrast to our findings are those of Steiner, Maimon, Palmer, and Kirsner,[9] Berkson, Walters, Gray, and Priestley,[10] and Blalock and Ochsner[11] who reported that the cure rate was higher in women than in men. Maimon, Palmer, and Kirsner[12] reported the survival rate to be unrelated to the duration of symptoms, or actually higher for those patients who have had symptoms the longest; our findings are in agreement. While one of the hopes for a better survival rate in gastric carcinoma has been based on early diagnosis, unfortunately, studies of long-term survivors do not indicate a direct relationship between short duration of symptoms and long survival. In contrast, the survival rate is greatest in those patients who have had symptoms for a long period before operation.

Summary

Twelve patients who survived 15 years or longer after operation for gastric carcinoma were studied clinically. Ten patients are still living, two died of causes apparently unrelated to the neoplasm. In this group there was neither evidence of recurrence nor postoperative development of distant metastasis. In one patient a second new primary carcinoma developed eight years after excision of the first one.

The presence of an abdominal mass did not contraindicate surgical treatment and did not preclude 15-year survival for two patients. Local lymph-node metastasis in five patients and local extension of the neoplasm did not prevent

long survival. Adequate resection when there is extension of the carcinoma to neighboring organs or when there are regional lymph nodes may still result in a cure.

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